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SKNy Worms and Long Life

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Interactions between insulin signaling and stress-response pathways can markedly impact life span. In this issue, Tullet et al. (2008) demonstrate that the worm homolog of Nrf2, called SKN-1, a transcription factor that switches on expression of antioxidant genes, is an important component of such signaling interactions.

The ability to adapt metabolic processes to environmental changes markedly influences life span in metazoans. Recent studies in a variety of model organisms are beginning to unravel the signal transduction networks involved in this adaptation. These studies suggest that integration of cytoprotective and stress-responsive signaling pathways with regulators of energy metabolism is crucial for environmental adaptation and hence for the control of longevity (Baumeister et al., 2006; Niedernhofer et al., 2006; Russell and Kahn, 2007; Wang et al., 2005).

As an evolutionarily conserved regulator of metabolism, the insulin/insulin growth factor (IGF) signaling pathway plays a central role in these signaling networks. Insulin/IGF signaling regulates life span in worms and flies, promoting growth and anabolic functions at the expense of cellular stress defenses and repair. An important mediator of these effects is the transcription factor Foxo, which is inhibited by insulin/IGF activity in favorable environments. In response to stress-responsive signaling pathways, however, Foxo is activated and stimulates the expression of genes that limit growth but mediate cellular repair. Elevated Foxo activity results in life span extension in worms and flies, supporting the idea that shifting energy resources from growth and anabolic functions to repair processes can influence fitness of the animal (Russell and Kahn, 2007). Reporting in this issue, Tullet et al. (2008) now identify a new node in the gene regulatory network downstream of insulin/IGF. Using biochemical and genetic approaches, these authors show that insulin/IGF signaling directly regulates SKN-1, the worm homolog of the transcription factor Nrf2, thereby affecting life span.

SKN-1/Nrf2 is a member of the cap-n-collar (cnc) family that induces expression of genes encoding antioxidant and detoxifying enzymes in response to oxidative stimuli. This function is widely conserved, with Nrf2 homologs in vertebrates and flies performing similar functions. Although the immediate consequence of Nrf2 activation is cytoprotection, in worms and flies elevated Nrf2/SKN-1 activity also results in increased stress resistance and extended life span (An and Blackwell, 2003; Bishop and Guarente, 2007; Sykiotis and Bohmann, 2008).

The function of SKN-1/Nrf2 during the response to oxidative stress and its evolutionarily conserved effects on life span are well documented, but the interaction of SKN-1/Nrf2 with other signaling pathways that influence stress tolerance and aging has remained unexplored. The new study by Tullet et al. (2008) now suggests that SKN-1/Nrf2 directly integrates insulin/IGF signaling and the stress response. The authors show that activation of insulin/IGF signaling results in phosphorylation of SKN-1 and subsequent retention of this transcription factor in the cytoplasm. This regulation parallels the effects of insulin/IGF signaling on Foxo, which

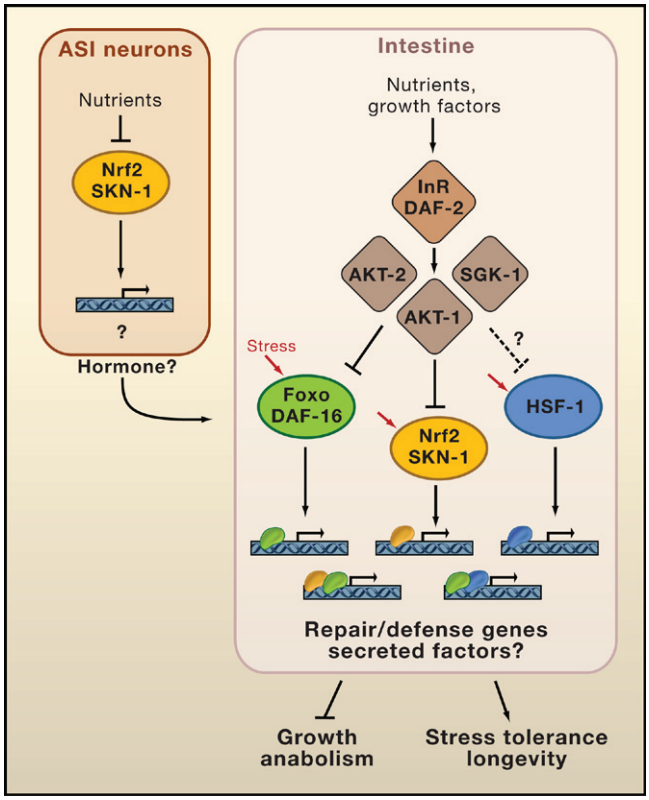

Figure 1. Regulating Life Span in the Worm
The Nrf2 homolog in *Caenorhabditis elegans*, SKN-1, acts together with DAF-16 and HSF-1 to regulate the expression of stress-response genes. All three transcription factors are required for life-span extension in the absence of DAF-2, indicating that they cooperatively regulate a transcriptional program that adapts metabolism and growth to environmental conditions. Distinct functions of SKN-1 in ASI chemosensory neurons and in the intestine regulate worm life span under conditions of dietary restriction and environmental stress, respectively.

is also phosphorylated and sequestered in the cytoplasm in response to insulin/IGF activity.

Tullet and colleagues find that translocation of SKN-1 to the nucleus is controlled by the insulin/IGF-responsive kinases AKT-1, AKT-2, and SGK-1. All three kinases are able to phosphorylate SKN-1 on multiple common and distinct sites. Confirming that this regulation affects SKN-1 activity, the authors show that the expression of a subset of SKN-1-responsive genes is induced when any of the three kinases are mutated. Induction of some of these genes is influenced by the presence or absence of DAF-16/Foxo, indicating partial coregulation of the transcriptional program downstream of insulin/IGF signaling by DAF-16 and SKN-1. Interestingly, similar transcriptional cooperation between DAF-16 and another stress-inducible transcription factor, heat shock factor 1 (HSF-1), has been reported (Hsu et al., 2003). A network of transcriptional regulators thus seems to act downstream of insulin/IGF signaling and distinct stress sensing pathways to fine-tune cellular stress responses to varying environmental conditions (Figure 1).

To test whether the interaction between insulin/IGF signaling and SKN-1 affects stress tolerance and longevity, the investigators assessed the survival of worms with loss-of-function mutations in SKN-1 and components of the insulin/IGF pathway. They show that SKN-1 is required for the stress tolerance and longevity phenotypes of worms lacking the insulin receptor DAF-2. This requirement is intriguing as it indicates that the longevity of *daf-2* mutant worms (which also requires DAF-16) is mediated in a parallel and nonredundant fashion by both DAF-16 and SKN-1. Accordingly, the authors demonstrate that overexpression of SKN-1 extends life span in a DAF-16-independent fashion.

Interestingly, SKN-1 is expressed in both the intestine and in the ASI chemosensory neurons of the worm (Figure 1). In both locations it affects life span, but apparently through quite different mechanisms. ASI neurons sense changes in food availability and provide endocrine signals that adjust metabolism to changing environmental conditions (Bishop and Guarente, 2007). Expression of SKN-1 in ASI neurons, but not in the intestine, is required for the life-span extension observed under conditions of dietary restriction, suggesting that the role of SKN-1 in these neurons is to regulate systemic responses to nutrition (Bishop and Guarente, 2007).

In contrast, in the intestine, which is the major fat storage tissue of the worm, SKN-1 responds to environmental stress and promotes expression of protective genes (An and Blackwell, 2003; Bishop and Guarente, 2007). Tullet et al. observed changes in the nuclear localization of SKN-1 and upregulation of SKN-1 target genes exclusively in the intestines of worm mutants with defective insulin/IGF signaling. Furthermore, they show that activation of SKN-1 in the intestine is sufficient to extend life span, suggesting that both the intestinal function of SKN-1 and its role in ASI neurons can influence fitness and aging of the worm, presumably through endocrine mechanisms. It is worth noting that similar effects on metabolic regulation and life span control by fat-storage tissues and neurosecretory cells are emerging in the fruit fly *Drosophila*. In flies, gain of Foxo function in the fatbody as well as in cells that produce insulin is sufficient to extend life span (Giannakou and Partridge, 2007; Wang et al., 2005). The Nrf2 homolog in flies called CnC is active in the intestine (Sykiotis and Bohmann, 2008), but it has not yet been established whether CnC might also act in fly neurosecretory cells. Further support for an evolutionarily conserved role for fat-storage tissues in life-span regulation comes from work in mice where loss of the insulin receptor specifically in adipose tissue extends life span (Russell and Kahn, 2007). It remains unclear, however, how endocrine interactions between adipose tissue and neurosecretory cells or the pancreatic β cells that produce insulin might influence life span in vertebrates.

An important question still to be addressed is the evolutionary conservation of the observed signaling interactions. Although Nrf2/CnC in *Drosophila* also promotes stress tolerance and longevity (Sykiotis and Bohmann, 2008), the activation of SKN-1 and Nrf2/CnC by stress is divergent. Human and *Drosophila* Nrf2 homologs are regulated by their binding partner KEAP (Kelch-like ECH Associated Protein 1), which sequesters Nrf2 in the cytoplasm under low-stress conditions (Sykiotis and Bohmann, 2008). In response to stress, the interaction between Nrf2 and KEAP is disrupted, resulting in nuclear translocation of Nrf2. In *C. elegans* (in which KEAP is not conserved), regulation of Nrf2/SKN-1 in response to stress is achieved by the stress-responsive MAP kinase p38, which phosphorylates SKN-1 and promotes its translocation to the nucleus (An and Blackwell, 2003). Thus, specific differences might also exist between worms and higher organisms in the regulation of Nrf2 by insulin/IGF signaling. Regardless of such mechanistic details, however, the general conservation of signaling networks linking stress responses with the control of metabolism suggests that interactions between insulin/IGF signaling and Nrf2 homologs may operate also in vertebrates, including humans. It will be critical to establish the significance and tissue specificity of such interactions, as it can be anticipated that they are important regulators of insulin function and thus influence metabolic homeostasis and the progression of age-related metabolic diseases.

REFERENCES

An, J.H., and Blackwell, T.K. (2003). Genes Dev. *17*, 1882–1893.

Baumeister, R., Schaffitzel, E., and Hertweck, M. (2006). J. Endocrinol. *190*, 191–202.

Bishop, N.A., and Guarente, L. (2007). Nature *447*, 545–549.

Giannakou, M.E., and Partridge, L. (2007). Trends Biochem. Sci. *32*, 180–188.

Hsu, A.L., Murphy, C.T., and Kenyon, C. (2003). Science *300*, 1142–1145.

Niedernhofer, L.J., Garinis, G.A., Raams, A., Lalai, A.S., Robinson, A.R., Appeldoorn, E., Odijk, H., Oostendorp, R., Ahmad, A., van Leeuwen, W., et al. (2006). Nature *444*, 1038–1043.

Russell, S.J., and Kahn, C.R. (2007). Nat. Rev. Mol. Cell Biol. *8*, 681–691.

Sykiotis, G.P., and Bohmann, D. (2008). Dev. Cell *14*, 76–85.

Tullet, J.M.A., Hertweck, M., An, J.H., Baker, J., Hwang, J.Y., Liu, S., Oliveira, R.P., Baumeister, R., and Blackwell, T.K. (2008). Cell, this issue.

Wang, M.C., Bohmann, D., and Jasper, H. (2005). Cell *121*, 115–125.